The clinical and translational prospects of microneedle devices, with a focus on insulin therapy for diabetes mellitus as a case study

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1.0 Abstract

Microneedles have the clinical advantage of being able to deliver complex drugs across the skin in a convenient and comfortable manner yet haven’t successfully transitioned to medical practice. Diabetes mellitus is a complicated disease, which is commonly treated with multiple daily insulin injections, contributing to poor treatment adherence. Firstly, this review determines the clinical prospect of microneedles, alongside considerations that ought to be addressed before microneedle technology can be translated from bench to bedside. Thereafter, we use diabetes as a case study to consider how microneedle-based-technology may be successfully harnessed. Here, publications referring to insulin microneedles were evaluated to understand whether insertion efficiency, angle of insertion, successful dose delivery, dose adjustability, material biocompatibility and therapeutic stability are being addressed in early stage research. Moreover, over 3,000 patents from 1970-2019 were reviewed with the search term ‘“microneedle” AND “insulin”’ to understand the current status of the field. In conclusion, the reporting of early stage microneedle research demonstrated a lack of consistency relating to the translational factors addressed. Additionally, a more rational design, based on a patient-centred approach is required before microneedle-based delivery systems can be used to revolutionise the lives of people living with diabetes following regulatory approval.

Keywords: microneedles, diabetes mellitus, clinical translation, patents, patient-centred design, insulin

2.0 Introduction

The recent increase of research in the field of microneedle technology presents the opportunity to address the shortcomings of subcutaneous injections and transdermal patches. Considered as a hybrid between the hypodermic needle and the transdermal patch, microneedles are biomedical devices that consist of arrays of micro-projections on a supporting base, with a height in the range of 250 to 1000 µm (Sabri et al., 2019). Upon insertion, the formation of aqueous channels across the *stratum corneum* allows both small drug molecules and large macromolecules to enter into and across the skin (Kirkby et al., 2020). Importantly, a notable advantage of all microneedles from the patient's perspective is the painless and minimally invasive application of the device to the skin. Despite a significant amount of research and microneedle devices becoming commonplace in the cosmetic sector, there remains significant barriers preventing microneedle devices from being approved for medical use (Kirkby et al., 2020).

One disease that has garnered considerable attention in microneedle research is diabetes mellitus. Diabetes is a complicated and debilitating illness, characterised by a partial or complete loss in the ability of the β-cells in the Islets of Langerhans, within the pancreas, to produce a suitable quantity of insulin to effectively regulate blood glucose concentration (American Diabetes Association, 2004). This presents immediate, dangerous risks for patients, such as diabetic ketoacidosis (DKA), alongside several severe long-term effects (Nyenwe and Kitabchi, 2016). Long-term effects are often categorised into macrovascular diseases, such as cardiovascular disease (CVD), cerebrovascular and peripheral vascular disease (PVD), and microvascular diseases, such as retinopathy, nephropathy and neuropathy (Nathan, 1993).

For many patients with a diagnosis of Type 1 Diabetes Mellitus (T1DM), multiple daily injections of insulin is the standard treatment option to effectively manage the condition (The Diabetes Control and Complications Trial Research Group, 1993). Compliance to these treatment regimens can be low, in part due to the use of traditional hypodermic needles, highlighting the potential for the clinical translation of microneedle technology (Peyrot et al., 2010).

In this review, the clinical translation of microneedle devices, using diabetes mellitus as a case study, is explored. Patents and publications for insulin-loaded microneedle devices will be critically evaluated in order to elucidate the steps which should be taken to enhance the chances of successful clinical translation. This review will be of value to those researching within the field of microneedle technology, particularly with a focus on diabetes mellitus, alongside clinicians who wish to understand more about the advantages and downfalls of microneedle technology.

3.0 Clinical translation of microneedles

There has been considerable progress within the field of microneedle research, driven by the need for a patient-centred approach to healthcare. Although not explored in this review, this includes the use of microneedles for diagnostic applications, which has not been overlooked within the field, as demonstrated in the 2021 review published by McAlister *et al* (McAlister et al., 2021). The clinical benefits alongside factors currently hindering clinical translation will be discussed in this section, with focus on the delivery of insulin, often used as model compound in transdermal delivery whilst also being a crucial treatment in diabetes.

3.1 Clinical Benefits

3.1.1 Simplicity and Ease of Administration

Given the minimally invasive nature of microneedles, such a delivery system can easily be administered by the patient themselves. Such an advantage obviates the need for a trained healthcare professional, or even carer, to help administer the therapeutic to the patient. Arya *et al* conducted a survey to evaluate and gauge the acceptability of microneedles following microneedle patch administration. In their work, Arya and co-workers discovered that 86% of the participants surveyed in their study were confident in self-administering microneedle patches and 93% of the participants displayed a preference for microneedle patches relative to a conventional hypodermic needle injection (Arya et al., 2017).

In addition, through judicious microneedle design and release kinetics, Chen *et al* designed an integrated microneedle system consisting of biocompatible cross-linked polymers of gelatine and hyaluronic acid loaded with short, intermediate and long-acting insulin. The microneedle system conferred a multiphasic release of insulin that covers the postprandial glycaemic excursions, thus maintaining a long-term euglycemia when evaluated *in vivo* using a diabetic rodent model (Chen et al., 2020). Besides that, some groups have developed smart microneedle systems that are capable of delivering insulin in response to blood glucose levels. For instance, a hydrogel-forming microneedle patch fabricated from boronate-containing hydrogel was designed by a research group led by Akira Matsumoto which displayed glucose-responsive properties. This microneedle system released insulin under hyperglycaemic conditions with negligible lag time and effectively switches off insulin release once the euglycemia has been achieved. Furthermore, such a microneedle system retained its needle architecture and structural properties even after seven days in an aqueous system, highlighting the potential for a long term sustained and responsive delivery of insulin (S. Chen et al., 2019). From a patient perspective, these integrated and smart yet simple to administer microneedle patches enable a simple once a day (or even once a week) administration as opposed to the conventional multiple daily insulin injections.

Furthermore, due to their miniature size, microneedle systems offer the possibility of therapeutic administration in a discrete fashion, especially in public settings. Such ease of administration overcomes the issues associated with conventional hypodermic syringes, which can be bulky, embarrassing and inconvenient to transport and use (Al-Tabakha and Arida, 2008).

3.1.2 Painlessness

One of the most prominent advantages of microneedles is the painless nature of application compared to conventional hypodermic needles. The level of pain experienced by the patient during microneedle application will have an impact on patients' acceptance of the technology and, ultimately, their compliance with treatment. Spain and co-workers conducted a survey that aimed at understanding the factors which led to the barriers to medication adherence and persistence in diabetes management. The group conducted a survey with 2000 patients with diabetes prescribed insulin, liraglutide, or exenatide. The researchers discovered that injection concerns which typically entails needle aversion and pain was the main reported barrier to medication adherence among those with diabetes (Spain et al., 2016). Painlessness may also be of great advantage in the paediatric population, who have a predisposition towards trypanophobia.

Despite the small sample size in their study (n=12), Henry *et al* was the first research group to report that microneedle treatment is not regarded as painful when applied to human volunteers (Henry et al., 1998). Observations were corroborated by anecdotal findings by Down and Harvey who also reported painless insertion of microneedles into human volunteers (Down and Harvey, 2002). Furthering this, Gill and co-workers investigated microneedle design factors that affect the pain scores in human volunteers. The group discovered microneedle length has a major influence relative to the number of microneedles on the participants' pain score. When the microneedle length was increased by 3-fold, from 450 µM to 1450 µM, the pain score increased by 7-fold. Meanwhile, a 10-fold increase in the total number of microneedles (of the same length), from 5 to 50 per array, only resulted in a 2-fold increase in pain score (Gill et al., 2008). An exploratory study by Birchall *et al* on the experience and perception of volunteers on the application of microneedle discovered that a majority of participants' surveyed described microneedle application as a pressing or heavy sensation on the skin in contrast to a stabbing sensation associated with hypodermic injection (Birchall et al., 2011). Since then, there has been a considerable body of evidence that has been gathered to demonstrate the painless nature of microneedle application in humans (Arya et al., 2017; Blicharz et al., 2018; Duarah et al., 2019).

In addition to almost painless administration, microneedle application typically results in minimal yet transient injection site damage (Bariya et al., 2012). Some of the most commonly reported side effects from microneedle patch application on human volunteers include tenderness, erythema and pruritus at the site of application (Rouphael et al., 2017). In addition, the length of microneedle applied to the skin is a crucial factor that affects the severity of the local side effects following microneedle application. This has been demonstrated by Bal *et al* who showed that the increase in length of microneedle (200, 300 and 400 µm) resulted in an increased level of erythema at the site of application (Bal et al., 2008). Nevertheless, these inflammatory responses are localised to the site of application and do not translate systemically, as evidenced by Vicente-Perez *et al* who showed no significant rise in sera biomarkers of inflammation (TNF-α and IL-1β) after repeated polymeric microneedle application (Vicente-Perez et al., 2017). The safety profile of microneedle application was further corroborated by the phase II clinical trial conducted by Zosano Pharma (National Institute of Health, 2021) and Corium (National Institute of Health, 2018) that showed the repeated application of coated titanium and dissolving polymeric microneedle did not cause any adverse reaction in the participants. Collectively these studies and clinical trials highlight the minimally invasive nature of microneedle application, along with its favourable safety profile.

3.1.3 Therapeutic Stability

It is frequently hypothesised that microneedles provide enhanced therapeutic stability and elimination of cold-chain storage requirements (Fukushima et al., 2011; Mönkäre et al., 2015).

Zhang *et al* explored the effect of incorporating insulin directly into the matrix of dissolving microneedles fabricated from maltose and alginate. The researchers discovered that incorporating insulin into the maltose-alginate paste followed by the two-step casting process of fabricating the microneedles did not alter the biological activity of insulin (Zhang et al., 2018). This work by Zhang and co-workers is also supported by findings from other research groups that showed incorporating therapeutics such as insulin into microneedles did not affect nor alter their biological activity (Chen et al., 2015; Fukushima et al., 2010; Yu et al., 2017).

Moreover, Ito *et al* reported that insulin, which was incorporated into dissolving microneedles fabricated from dextrin, displayed stability for up to one month even when the microneedles were stored at 40 °C. Such results were also observed by Ling *et al* who reported that when insulin is incorporated into dissolving microneedles composed of starch and gelatine, the protein was stable for up to one month even when stored at 37 °C. Since then, similar results have emerged from various research groups that highlight the stability of insulin being stored at room temperature once incorporated into microneedle formulations (Fonseca et al., 2020; Zhu et al., 2020). Such enhanced stability at room temperature upon incorporation into microneedles is not only limited to insulin but has also been demonstrated for other therapeutics ranging from antibodies (Mönkäre et al., 2015), vaccines (Hirobe et al., 2015) and small drug molecules (Lee et al., 2011; Zhang et al., 2012).

The mechanism for such enhanced stability is attributed to the presence of materials used to fabricate the needle matrix. These materials consist of synthetics, natural polymers or sugars, such as trehalose and maltose. Once a therapeutic, such as insulin, is incorporated into the microneedle matrix, the polymers form a molecular interaction with the therapeutic which suppresses molecular mobility of the incorporated molecule. This reduces the likelihood of recrystallisation, aggregation and phase separation occurring during storage. The restricted molecular mobility also reduces the kinetics of potential chemical and physical degradation reactions during storage (Choi et al., 2013; Sabri et al., 2019). Besides, the polymers and incorporated sugars also form a stabilising shell by replacing the removed water molecules around the incorporated therapeutic, which mitigates dehydration induced change upon storage (McGrath et al., 2014; Mistilis et al., 2016).

Providing the stability of the therapeutic can be guaranteed, this gives rise to the opportunity for the controlled release of therapeutics, as demonstrated by Wang *et al* with microneedles made from a modified silk fibroin which released insulin over 60 hours (Wang et al., 2019).

3.2 Unmet translational obstacles

3.2.1 Sterility

Sterility will be a key requirement for regulatory bodies as microneedles breach the outermost layer of the skin. This is of great importance, especially for patients with diabetes as they are at a greater risk of hospitalization and mortality resulting from viral, bacterial, and fungal infections (Erener, 2020). To produce microneedles intended for clinical use, it may be required that such products are terminally sterilised, which is the means of sterilisation favoured by regulators. If such a process is incompatible, the product may need to be manufactured under aseptic conditions. From a commercial standpoint, the method of sterilisation will be critical as this will impact the cost of the final product.

McCrudden *et al* were the pioneers who first explored sterile manufacture of microneedles. In this work, the group fabricated two types of microneedle systems- dissolving and hydrogel-forming microneedle patches. The group discovered that terminal sterilisation techniques such as steam autoclaving and dry sterilisation damaged the fabricated microneedle system (Mccrudden et al., 2014). This is attributed to the hygroscopic nature of the hydrophilic polymers used in fabricating the polymeric microneedle arrays. Nevertheless, the group discovered that aseptic production and gamma irradiation may be viable alternatives to sterilise the fabricated microneedle system. McCrudden and co-workers discovered that hydrogel-forming microneedles were structurally unaffected by the dose of gamma irradiation, which was 25 kGy (2.5 Mrads), with the resulting microneedles displaying endotoxin levels below 20 units/device, which corresponds to FDA guidelines for medical devices that are in contact with cardiovascular or lymphatic tissue. However, this method of sterilisation altered the drug content and release profile for dissolving microneedles, which implies that gamma irradiation may not be a viable method of sterilisation for dissolving microneedles (Mccrudden et al., 2014).

Furthering this, Swathi *et al* explored the effect of gamma irradiation on dissolving microneedles. Four different dissolving microneedles systems fabricated from sodium carboxymethyl cellulose (CMC), polyvinylpyrrolidone (PVP) K30, PVP K90 and sodium hyaluronate (HU) were evaluated. Upon exposure to gamma irradiation, it was discovered that the mechanical properties and architecture of the needles of CMC and PVP K30 were affected. However, the appearance, properties and release profile of PVP K90 and HU were unaffected by the dose of gamma irradiation used (Swathi et al., 2020). This study suggests gamma irradiation is still a viable approach to sterilise dissolving polymeric microneedles. However, formulation scientists ought to be judicious in choosing the polymer used to fabricate the microneedle system, ensuring that it is compatible with the method of sterilisation.

Going forward, the use of self-sterilising biomaterials, such as silver coated microneedles, may be able to provide a potential solution to developing a sterile microneedle system (Knetsch and Koole, 2011; Pappas et al., 2015).

Overall, these seminal studies have highlighted that gamma irradiation may be the method of choice for terminal sterilisation of microneedles at a commercial scale. However, in instances where sensitive or thermolabile biologics are loaded, including insulin, gamma irradiation may not be suitable and alternative method of ensuring sterility may need to be considered.

3.2.2 Reproducibility of insertion and feedback

Another aspect that must be considered is the ability of the microneedle systems to be inserted into the skin in a controlled and reproducible manner. Indeed, the insertion of microneedles into the skin is a multifactorial process ranging from design and material dependent factors to the viscoelastic nature of the skin. Indeed, in 2004 Davis *et al* demonstrated that a force of 0.1 – 3 N was sufficient to insert a single hollow or solid MN, dependant on the tip cross-sectional area of the MN, supporting the feasibility of inserting MNs by hand (Davis et al., 2004).

One of the ways to ensure effective and reproducible insertion of microneedle patches into the skin would be the use of applicators. Van der Maaden *et al* explored the effect of using either manual or impact insertion technique on individual variability of microneedle insertion onto *ex vivo* human skin from 15 volunteers. The group discovered that an impact insertion applicator that applied the microneedle at a constant and reproducible velocity of 3 m/s resulted in reproducible microneedle insertion with high penetration efficiency (Van Der Maaden et al., 2014a).

Since then various groups have explored the design of several applicators to improve the insertion and reproducibility of microneedle application to the skin. For instance, Leone *et al* developed a digitally controlled microneedle applicator which enabled microneedle insertion through either impact insertion or manual/force insertion. The group developed a universal microneedle applicator and evaluated the use of the device in inserting six different microneedle systems of different geometry, length and material. It was discovered that using impact application, the penetration efficiency of the six microneedle systems was close to 100%, while 80% penetration efficiency was achieved using manual/force insertion. Such findings corroborated the initial study conducted by Van der Maaden and co-workers. Leone *et al* also discovered that the presence of a curved backing layer for dissolving microneedle patches resulted in an improved insertion efficiency than microneedle patches with a flat backing layer. The researchers attributed this finding to the presence of a convex surface that positioned the microneedle at an optimal angle towards the skin surface, which ultimately improves the capability of the microneedle to penetrate the skin (Leone et al., 2018). Given the importance of inserting the microneedles in a reproducible and accurate fashion, several companies have developed and continue to develop a variety of microneedle applicators. Although most of these applicators are still in the development stage, some of these devices are commercially available, including MicroCor^{TM} and Macroflux®. For a more detailed review of the range of microneedle applicators that have and are currently being developed, readers are signposted to the publication by Sigh *et al* that reviewed the patents on various microneedle applicators (Singh et al., 2011).

Moreover, through engagement with potential end-users, Donnelly and co-workers have identified that one of the key issues with translating microneedle systems is the uncertainty in the successful application of the microneedle into the skin (Donnelly et al., 2014a). Therefore, in addition to providing reproducible and controlled insertion upon application, it is also of great importance that the end users (e.g. patient or carer) are given an indicator that they have successfully inserted the microneedle into the skin. For instance, Norman *et al* reported the use of a simple, low-cost snap-based device that provides audible feedback upon microneedle application. The group discovered that there was a significantly higher end-user preference for microneedle systems that incorporated the audible snap-based feedback system relative to microneedle systems that did not have such feedback system (Norman et al., 2014). Furthering on the idea of incorporating a feedback system into the microneedle device, Vicente-pérez *et al* explored the use of a low-cost pressure-indicating sensor film

(PISF), Pressurex-micro® Green attached to the backing layer of the microneedle system as a feedback system to indicate successful microneedle insertion. The film undergoes a colour change when a pressure of greater than 18.6 Ncm^{-2} has been applied to the skin, which is sufficient for successful microneedle insertion. The group recruited 20 volunteers to participate and evaluate the use of such a system and discovered that 75% of the participants displayed a preference for the incorporation of PISF within a microneedle device (Vicente-pérez et al., 2016).

In short, for microneedles to be successfully translated into clinical practice, the design of the system must ensure microneedles can be inserted into the skin in a consistent and reproducible fashion, whilst also ideally providing the user feedback that the system has been applied correctly. Moving forward such requirement may be achieved if the PISF (or alternative feedback system) is incorporated within microneedle applicators.

3.2.3 Adjustability and dosing consistency

A factor key to the successful clinical acceptance of microneedles is dose adjustability. An example where this is key is that of insulin. T1DM patients must be able to inject a precise dose of insulin, which is a consideration that is poorly addressed in microneedle literature. Such neglect in design remains a sizeable barrier from a clinical standpoint given doses vary between patients and may preclude certain types of microneedles from being used. For instance, given the microneedles are likely to be loaded with a predetermined quantity of drug during the manufacturing process, coated and polymeric microneedles may be particularly unsuitable due to the inability to alter the drug loading prior to application to the skin. Moreover, whilst the quantity of drug applied to the skin after the insertion of solid microneedles may be altered it is likely that this would be an inaccurate and unreliable way of administering a precise dose to the systemic circulation and so unlikely to be approved by regulatory bodies.

Despite the drawbacks with other microneedle classes, there remains hope that hollow microneedles may be more suited to this role, with one option being the attachment of hollow microneedle to a device similar to marketed devices, such as pre-filled pens. Moreover, analyte-responsive microneedles may be able to address the dose variability requirement by only releasing the required quantity of drug in response to the analyte concentrations in ISF. However, such bioresponsive systems still suffer issues with safety and approval from regulators as such complex systems typically employ novel polymers which have limited safety data.

More innovative approaches have been suggested to overcome dose adjustability, including patients timing how long microneedles are applied to the skin for or cutting microneedle patches to tailor the dose, however these carry an increased risk of under or over-dosing.

Furthermore, it must be demonstrable to the regulators that the full dose of the drug has been delivered to the patient before regulatory approval. It is frequently reported that the penetration depth of microneedle into the skin is much shorter than the length of the microneedle itself (Martanto et al., 2006). This may pose a problem in delivery efficiency, particularly with dissolving microneedles, as incomplete microneedle insertion may result in incomplete delivery of the dose. In order to circumvent this issue one strategy that could be utilised is to only load the therapeutic agent at the tip of the microneedle as this will provide the best chance of complete dose delivery (Peng et al., 2021). Nevertheless, this strategy does suffer the issue of drug migration from the needle tip into the backing layer, which may limit the amount of drug delivered across the skin. Furthermore, such a strategy may also restrict the quantity of a therapeutic agent that can be loaded. In addition, the ability to deliver the drug effectively is linked to the reproducibility of inserting microneedles into the skin.

Should complete dose delivery be deemed impossible, then an acceptable range of delivery efficiency ought to be standardised as a benchmark for microneedle-based delivery systems. Such a benchmark would be a reasonable compromise, particularly for vaccines, accounting for the anatomical skin physiology and elasticity that may result in incomplete dose delivery but may preclude certain drugs with a narrow therapeutic window.

Analytical techniques and computer modelling systems, such as finite element analysis (FEA) are powerful tools, the popularity of which are rapidly advancing, potentially aiding the rational design and certainty that drug will be consistently delivered at an early research stage (Sabri et al., 2020; Yadav et al., 2020). However, to date, many of the models used are overly simplified and do not provide an accurate representation of microneedle insertion into the skin. Partly this is due to the lack of availability of the prerequisite data required for building an accurate model, which is timely and arduous to collect. This includes quantitative data for the skin's multiple strata, which exhibit different properties, such as elasticity, density and strength. Moreover, FEA analysis will only give data at nodal points, meaning not all the weaknesses in a system may be identified. In addition, most of these FEA analyses have been focussed on the analysis of single microneedle insertion into the skin, not reflecting the popularity of microneedle arrays (Davis et al., 2004).

Published in 2021, Feng *et al.* demonstrated that the stability and diffusion properties of two different insulin-containing MN systems could be studied using all-atom molecular dynamics and coarse-grained dissipative particle dynamics simulations (Feng et al., 2021). Importantly, this work demonstrated a difference in the affinity of insulin to hyaluronic acid compared to polyvinyl alcohol, which could affect the deliverable dose *in vivo* and the insulin pharmacokinetic profile. Utilising these kinds of simulations during early-stage research may help ensure that the material choice favours full payload release and improves dosing consistency.

Collectively, until dose adjustability and consistent dosing are perfected, it is accepted that microneedle technology for insulin administration will not be approved by the regulators (Asakura and Seino, 2005).

3.2.4 Sharps waste and disposal upon use

Another challenge is the disposal of microneedle systems post-application.

Within a clinical setting, the disposal of sharps, such as hypodermic needles, follows a structured pathway where specific bins are removed by specialised waste contractors. On the other hand, needle use and disposal by patients who self-administer their medication is a far more complex situation as some patients may underestimate the severity of sharp hazards and dispose needles via domestic waste routes (Costello and Parikh, 2013). Furthermore, the additional cost of providing, collecting and disposing specialised sharps containers is another factor to consider in the overall treatment cost for patients receiving injection-based therapies.

Although microneedles are small in comparison to hypodermic needles, these micron size needles are still capable of puncturing the skin thus presenting a potential sharps risk during handling and disposal. This is further exacerbated by the fact that once inserted into the skin, microneedles will be in contact with patient tissue and dermal microcirculation and subsequent removal of the microneedles poses a potential risk of contamination of blood or interstitial fluid. Such concern is corroborated by the FDA and Public Health England over the use of microneedle rollers in cosmetic practice (Public Health England, 2017; US Food and Drug Administration, 2020).

With regards to sharps disposal, solid, coated and hollow microneedles still possess the risk of sharps injury, as the microneedles are still removed intact post-application giving rise to the risk of reinsertion (McConville et al., 2018). Furthermore, the minimally invasive and painless nature of microneedle insertion may result in such accidental re-insertion going unnoticed as opposed to needle stick injuries involving conventional hypodermic needles. Under such circumstances, there will be no follow-up diagnosis and treatment which could lead to blood borne pathogen transmission going undetected.

Such issues may be overcome via the use of dissolving or hydrogel-forming microneedle as these microneedle variants are self-disabling (preventing reinsertion) upon skin application, reducing the likelihood of needle stick injuries post application. This also addresses concerns about the unadvisable reuse of needles (Becton-Dickinson, 2006). In addition, the issues associated with sharps disposal of conventional hypodermic needles will be circumvented. These types of microneedle patches are, to some degree, like traditional transdermal patches, where the patient can just fold the patches and discard them in household waste without the need for a specialised waste container.

3.2.5 Material biocompatibility

As the microneedles breach the *stratum corneum*, it is integral that the material selected is biocompatible. Such materials need to possess properties that allow the microneedle to be inserted and remain in situ with a minimal immunogenic response from the surrounding skin tissues. This is of great importance particularly in the management of diabetes, which is a chronic disease and would require repeated microneedle application to deliver therapeutics across the skin compared to the potential one-off application of microneedles, such as for the delivery of a vaccine.

Early research in the field of microneedles involves the use of microneedles fabricated from silicon, stainless steel and ceramics either as solid microneedles (McAllister et al., 2003), hollow microneedles (Baron et al., 2008) or as a vehicle to deliver therapeutics for coated microneedles (McGrath et al., 2011). However, silica and ceramics are known to be brittle materials which give rise to concerns on the likelihood of microneedle tip breakage and deposition into the skin. With regards to silicon, the biocompatibility of the material is still uncertain and there is conflicting evidence on the safety profile of using silicon for biomedical applications. Bayliss and co-workers demonstrated that nanocrystalline silicon did not display significant cytotoxicity when exposed to Chinese hamster ovary (Bayliss et al., 1997). In contrast, there is evidence that suggests the use of silicon-based material in biological tissues may lead to the formation of granulomas due to the release of silicon from the material into the surrounding tissues (Kubo et al., 1997; Millard and Maisels, 1974). On the other hand, ceramics, including Ormocer® (organically modified ceramics) and calcium-phosphate based ceramics, display a much better safety profile as materials for biomedical application (LeGeros, 2002; Ovsianikov et al., 2007). Similarly, metals used in the fabrication of microneedles are typically biocompatible, especially 316L stainless steel (Chen and Thouas, 2015). In addition, the widespread use and acceptance of stainless steel in medical devices further corroborate the biocompatibility of using this material to manufacture microneedles (Niinomi, 2002). Moreover, platinum (Cowley and Woodward, 2011), titanium (Sidambe, 2014) and palladium (Manam et al., 2017) based alloys are also deemed biocompatible and safe for biomedical application.

In addition to inorganic materials, there has been a considerable rise in the use of natural sugars and carbohydrates along with synthetic polymers to fabricate and manufacture microneedles. This is attributed to the shift in microneedle research from solid, coated and hollow microneedles towards the use of dissolving and hydrogel-forming microneedles. Maltose, sucrose, sorbitol, trehalose, xylitol and galactose are examples of FDA approved materials that have and could be used in microneedle production (Apollo et al., 2018; Pere et al., 2018; Raphael et al., 2016). Although these materials are considered innocuous and safe for microneedle application and production, certain sugars such as xylose, galactose and maltose have been reported to interfere with blood glucose monitoring which could be an issue in patients with diabetes (Floré and Delanghe, 2009; Galante et al., 2009). Furthermore, the difficulties associated with fabricating microneedles from simple sugars, which include high processing temperatures, low drug loading, sterilisation, along with poor insertion profile are likely to prevent successful clinical application of simple sugar-based microneedles (Donnelly et al., 2009). It is worth considering the potential reluctance of diabetes patients to administer sugar-based microneedle systems even if such microneedle systems are proven to be clinically safe. Such reluctance may arise from the fears that applying sugar-based microneedles may cause a spike in blood glucose level. Should such fears arise, the role of the pharmacist along with other healthcare workers may be pivotal in educating the patient that the dose of sugar applied to the skin is low compared to the typical sugar consumed from food along with the difference in type of sugar which is used to fabricate the needles.

Additionally, polysaccharides have been investigated for microneedle fabrication, including cellulose derivatives (Park et al., 2016), chitosan (Chen et al., 2013), alginates (Zhang et al., 2018) and hyaluronic acid (Hao et al., 2018), starch (Ling and Chen, 2013) and dextrin (Ito et al., 2006). In addition to being

FDA approved materials, these polysaccharides are considered biocompatible as they display chemical motifs that are identical or similar to the composition of the human extracellular matrix (Shelke et al., 2014). Moreover, some of these materials such as hyaluronic acid, chitosan and dextrin are biodegradable and broken down into non-toxic residues thus obviating issues associated with material accumulation in biological tissue (Croisier and Jérôme, 2013; Hreczuk-Hirst et al., 2001; Zhong et al., 1994). A recent study completed by Zhang *et al.* further supports that hyaluronic acid may be a suitable material for manufacture of MNs owing to a lack of erythema at the insertion sites and no histopathological abnormalities after the administration of a MN patch daily for 90 days when tested in a murine model (Zhang et al., 2021a).

Synthetic polymers have also been frequently employed as materials used to fabricate microneedles. Some of these polymers include polyvinyl alcohol (PVA) (McCrudden et al., 2014), polyvinyl pyrrolidone (PVP) (Quinn et al., 2015), polylactic acid (PLA) (Terashima et al., 2019), polyglycolic acid (PGA) (Boehm et al., 2015), poly(lactic-co-glycolic) acid (PLGA) and poly(methyl vinyl ether-co-maleic anhydride) (Donnelly et al., 2014b). In addition to being extensively used in the area of drug delivery, these polymers display excellent biocompatibility, overcoming immune mediated foreign body response upon microneedle application (Larrañeta et al., 2016). In terms of elimination following *in vivo* application, PLA, PGA and PLGA are biodegradable. Therefore these polymers will be broken down following skin application into the smaller glycolic and lactic acid, which are then excreted from the body (Larrañeta et al., 2016). For poly (methyl vinyl ether-co-maleic anhydride), this polymer is typically cross-linked with glycerol to develop hydrogel-forming microneedles. This cross-linked polymer swells upon skin application and is completely removed intact from the skin post-application thus overcoming issues of polymer deposition post application (Donnelly et al., 2014b). Even so, a study completed by Al-Kasasbeh *et al.* gave a positive indication for the safety of the PEG crosslinked PMVE/MA hydrogel MNs after repeat application on human participants (Al-Kasasbeh et al., 2020).

On the other hand, for polymers such as PVP and PVA, which undergo a slower rate of biodegradation, the polymer will likely be slowly excreted from the body. Based on the research conducted by Kagan *et al* on the elimination of macromolecules following administration to the skin, it is estimated that a majority of the polymers with molecular weights below 66 kDa will be drained into the dermal blood capillaries with minimal drainage into the dermal lymphatics before reaching the systemic circulation (Kagan et al., 2007). Upon reaching the systemic circulation, should the polymer display a molecular weight of less than 60 kDa, the polymer will be excreted through the kidneys following glomerular filtration (Hespe et al., 1977; Yamaoka et al., 1995). These findings were further supported by a study conducted by Zhang *et al*., who inserted MNs manufactured from PVA into mice daily for 160 days and found no evidence of toxicity but did find the concentration of PVA reduced in skin over time, suggesting ‘dissolution, diffusion or degradation of PVA in the skin’ (Zhang et al., 2021b).

Whilst the obstacles highlighted in this section may currently seem insurmountable, microneedles may still offer a valuable drug delivery platform in many clinical conditions, including diabetes mellitus.

4.0 A case study: diabetes mellitus

Diabetes mellitus is a metabolic condition characterised by impaired insulin secretion and/or action, resulting in chronic hyperglycaemia. As of 2021, the International Diabetes Federation have stated that approximately 537 million adults worldwide are diagnosed and living with diabetes mellitus (International Diabetes Federation, 2021). This has been estimated to increase to 570.9 million worldwide by 2025 (Lin et al., 2020). With so much clinical prospect, it is clear microneedles could transform diabetes care.

4.1 The impact of diabetes mellitus

4.1.1 The burden of diabetes mellitus on healthcare systems worldwide

There are multiple forms of diabetes mellitus however the most common are known as Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM), accounting for 1.8% and 98.3% of cases worldwide in 2017 (Liu et al., 2020; Soh and Topliss, 2014).

T1DM is classically referred to as juvenile-onset diabetes due to typically being diagnosed in patients at a young age. In this form, the pancreatic β-cells are subject to damage either by T-cell mediated autoimmune destruction (Type 1A) or idiopathic (Type 1B) (Burrack et al., 2017). This results in an inability to produce insulin (Atkinson et al., 2014). Worldwide, the incidence of T1DM has been increasing for multiple decades (Mobasseri et al., 2020; You and Henneberg, 2016).

Conversely, T2DM is more commonly diagnosed in patients of advancing age and is known to be of a higher incidence in those with poor lifestyle choices and health, alongside a strong genetic component (Zheng et al., 2018). Cells may become less responsive (resistant) to insulin whilst the quantity secreted is not increased sufficiently, meaning blood glucose levels are not adequately lowered (Hackett and Jacques, 2009). Incidence is predicted to further increase over the coming years, attributed to global changes in lifestyle (Saeedi et al., 2019).

Long-term damage caused by uncontrolled diabetes is severe and intrinsically linked with the magnitude and duration of hyperglycaemia, in conjunction with other pre-disposing patient factors. It is forecasted that 57.9% of patients with T2DM will develop one or more complications in their lifetime (American association of clinical endocrinologists, 2006).

In 2015 $1.3 trillion USD was spent on diabetes worldwide, which is anticipated to increase to $2.1 trillion USD by 2030, alongside disease prevalence (Bommer et al., 2018). Moreover, the Global Burden of Disease Study from 2017 revealed that T1DM and T2DM are a leading cause of disability worldwide, alongside being responsible for the fourth highest cause of 'years lived with disability (YLD)', further demonstrating the heavy social and economic burden associated with diabetes.

4.1.2 Current treatment options in diabetes

To achieve optimal blood glucose control, most patients with T1DM are initiated on a basal-bolus insulin regimen from diagnosis (American Diabetes Association, 2020; Nathan, 2014; NICE, 2005). This regimen not only adequately replaces the insulin the pancreas is unable to produce but aims to mimic the natural secretion of insulin in response to food intake that would occur in a healthy individual. The regimen is made up of long-acting insulin, which is injected once or twice daily as the basal dose, with quick-acting insulin, injected prior to carbohydrate intake with the dose altered depending on the carbohydrate content of the food being eaten and pre-food blood glucose levels.

If patients are not suited to this style of regimen another option available is twice or three times daily injections of premixed insulins, containing solutions of both long-acting and quick-acting insulin (NICE, 2005). This is most commonly prescribed for patients who fail to self-administer their insulin consistently and aims to reduce the number of injections required; however it is less targeted and unable to produce the optimal management as with the basal-bolus regimen. A third option is for the patient to use one injection of long-acting insulin with one injection of a pre-mixed isophane insulin to provide insulin that will act throughout and prevent dangerously high blood glucose levels (NICE, 2005). Despite these options, a proportion of patients continue to struggle to effectively control their blood glucose, risking repeatedly being admitted to the hospital. For these patients, insulin pumps may be a viable treatment option as the blood glucose levels are continuously monitored and insulin administration is adapted in real-time (Ginsberg, 2019).

Unlike in T1DM, patients with T2DM can often be managed with dietary and lifestyle interventions, then oral pharmaceutical agents. Currently, the American Diabetes Association and the European Association for the Study of Diabetes recommend metformin as the first-line oral agent when diabetes is unsuccessfully controlled through lifestyle choices (American Diabetes Association, 2020; Inzucchi et al., 2015; NICE, 2020). If metformin alone does not provide adequate control, therapy can be intensified through the addition of one or two oral agents from the following classes of medications: sulfonylureas, thiazolidinediones, dipeptidylpeptidase-4 (DPP-4) inhibitors, sodium glucose co-transporter 2 (SGLT-2) inhibitors and, more recently, oral GLP-1's. If oral triple therapy is still unsuccessful, a subcutaneous GLP-1 receptor agonist may be prescribed as the third agent in a triple therapy combination. Insulin therapy may also be considered in T2DM patients, particularly if blood glucose remains uncontrolled (American Diabetes Association, 2020; NICE, 2020).

4.2 Limitations with current insulin treatment

Poor compliance and adherence to medications is not a new issue to the pharmaceutical industry or healthcare providers. Moreover, it will come as no surprise that patients with diabetes are frequently non-compliant with their prescribed medications. However, with such severe long-term consequences, compliance should be encouraged, and medication regimens personalised where appropriate to encourage acceptance from patients (EMA, 2016; Lambrinou et al., 2020).

Multiple studies have shown that T1DM patients struggle to adhere to their therapeutic regimen and this has been attributed to lifestyle challenges, as shown by Peyrot *et al*, as well as medication side effects, demonstrated by García-Pérez *et al* (Cramer and Pugh, 2005; García-Pérez et al., 2013; Peyrot et al., 2010; Polonsky and Henry, 2016). However, many of these studies are conducted in the USA and, therefore, it should be considered that there may be differences in healthcare provision internationally, which may affect patient experience, education and cost of treatment (Davies et al., 2013).

Moreover, needle phobia should not be underestimated as a significant factor in non-compliance with insulin treatment. Karter *et al* found that 13% of patients who were newly prescribed injectable insulin yet non-adherent to their regimen cited needle phobia as a reason for this (Karter et al., 2010). Later, in a review authored by Kruger *et al*, it was demonstrated that both needle length and gauge play a key role in the perception of how painful an injection may be (Kruger et al., 2015). Despite sizeable research around needle development already having taken place, such as the finding that insulin pen needles are less susceptible to needle blunting, therefore reducing pain upon insertion into the skin and being preferable for patients, there remains a sizeable negative stigma around the regular use of injections (Logan Stotland, 2006). The findings of Kruger *et al* demonstrate that with innovative modifications to transdermal drug delivery devices compliance to insulin therapy may be improved.

5.0 Clinical translation of insulin-loaded microneedles

Aside from its clinical value, insulin is an example of a highly potent therapeutic, a favourable characteristic in terms of drug loading, explaining why the protein is a popular model compound used in microneedle research. Below we focus on the subtypes of microneedles, as seen in Figure 1, how insulin has been utilised in these systems and why these microneedle systems have not yet made it to fruition.

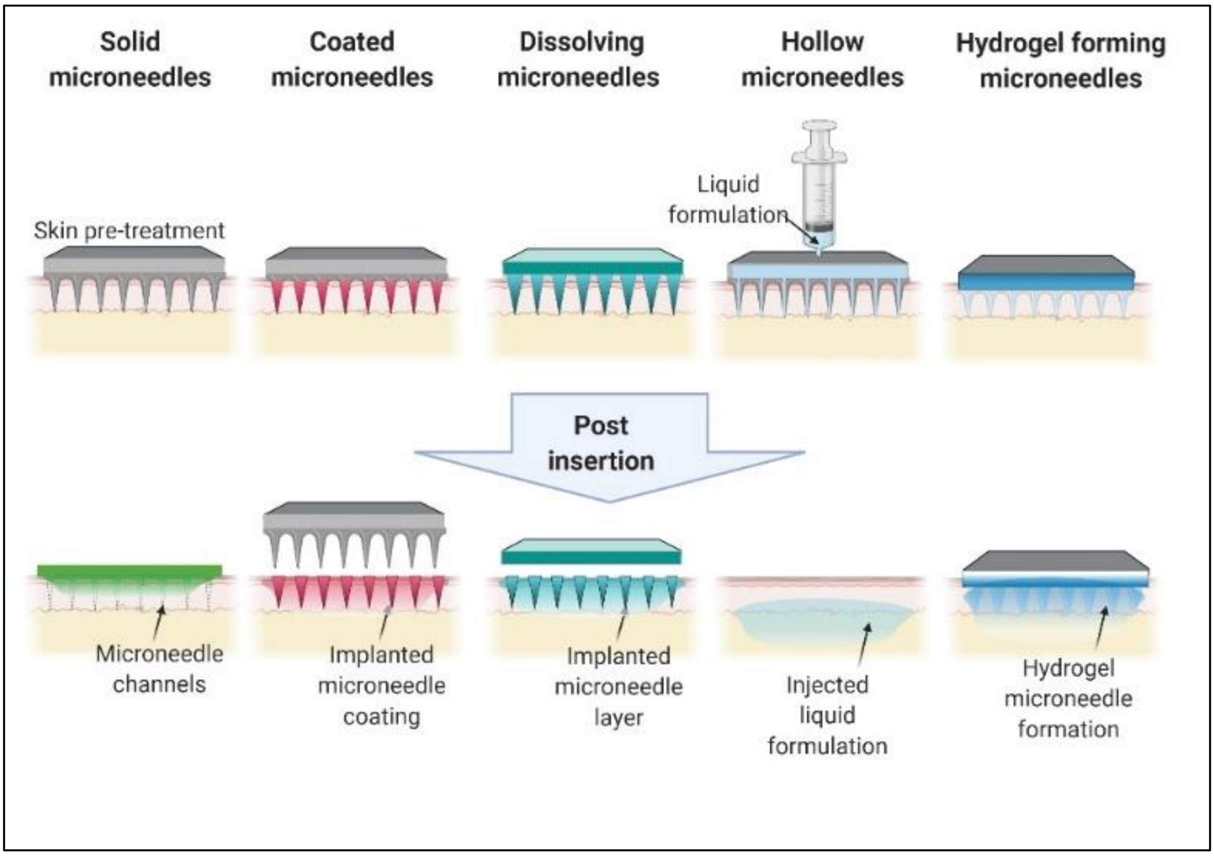


Figure 1: Types of microneedles with their structure pre and post-insertion into human skin

5.1 Suitability of microneedle subtypes for insulin

Solid microneedles consist of fine arrays of micron length needles fabricated from either silicon, stainless steel or biocompatible polymers. The ‘poke-and-patch’ approach using solid microneedles was the earliest microneedle-based drug delivery strategy, which involves a two-step application process of microneedles as a skin pre-treatment followed by the application of drug formulation. Such a two-step application is limited by the duration in which microneedle channels remain open, which could be as short as 15 minutes (Bal et al., 2010). This may severely limit the quantity of therapeutic delivered, a risk that is not appropriate when administering any drug with a narrow therapeutic window, including insulin. In addition, any drug delivery strategy that necessitates the use of more than one application step is unlikely to be accepted by the majority of patients, leading to poor medication adherence (Osterberg and Blaschke, 2005).

Coated microneedles are a modified version of solid microneedles that contain an additional drug-polymer coating. Upon insertion into the skin, the microneedle is left in place over a set period to allow the coating to dissolve, leading to drug release. This strategy is suitable for administering a bolus dose of drug but is particularly suited for a dermal or transdermal target (Gill and Prausnitz, 2007). This simple one-step application process avoids the problem of formulation misalignment with microneedle perforated skin, as seen with solid microneedles.

However, one of the disadvantages of coated microneedles is the limited amount of drug which can be coated onto the tip and shaft (Gill and Prausnitz, 2007). Additionally, concerns have been raised on how well the coating adheres to the microneedle upon insertion into the skin, causing concern that coating may flake off prematurely before piercing the skin, leading to unwanted loss of therapeutics. Nevertheless, several strategies have been explored to ameliorate such drawbacks. For instance, Gill *et al* found that increasing the insertion speed and tailoring the microneedle design (by fabricating a pocketed microneedle) may help improve coated microneedle delivery of therapeutics while reducing the propensity of coat flaking during insertion (Gill and Prausnitz, 2007). Despite this, careful consideration should be given to whether a suitable quantity of insulin can be loaded into this system for it to be of clinical value to those with diabetes.

Dissolving microneedles encapsulate drugs within a polymeric matrix, forming the needles themselves. Unlike coated microneedles, the entire microneedle shaft dissolves upon insertion into the skin, resulting in no biohazardous sharps post insertion. The meticulous design of the microneedle matrix permits the drug delivery profile to be tuned for bolus or even sustained release over several weeks (Bediz et al., 2014; Demuth et al., 2013; Lee et al., 2008).

However, in meeting such requirements, the microneedle needs to be inserted into the skin for a specified period before being removed. Such insertion time may vary from as little as one minute to as long as an hour for effective dissolution (Lee et al., 2008; Sullivan et al., 2008). To ensure patients received their recommended dose of insulin, careful counselling would be needed by healthcare professionals and pharmacists to ensure the correct application and removal. Furthermore, the deposition of polymer within the skin post-insertion has raised safety concerns. This is of particular concern if such systems are to be used in the management of chronic conditions, such as diabetes. However, various groups have circumvented this issue via utilising regulatory approved biodegradable polymers, which degrade via hydrolysis into non-toxic molecules over time (Donnelly et al., 2012b).

Hollow microneedles are reminiscent of hypodermic injections as they facilitate the flow of therapeutics via the microneedle bore into the skin. This approach permits more control over drug delivery rate by pressure driven flow (Prausnitz, 2004). Unfortunately, the complex manufacturing requirements, susceptibility to fracture and risk of needle stick injury are notable limitations of hollow microneedles (Hong et al., 2014). Additionally, dermal tissue blockage at the microneedle tip upon insertion is another drawback of these microneedles. Nevertheless, such problems have been resolved via partial microneedle retraction post-insertion, which induces tissue relaxation thus enhancing fluid infusion (Martanto et al., 2006; Wang et al., 2006). It should be noted, the retraction of microneedles to promote fluid infusion has been associated with increased pain sensation and may promote interstitial fluid moving into the lumen of the microneedle, increasing resistance to the delivery of the medicament (Gupta et al., 2011).

Finally, hydrogel microneedles are the latest class of microneedle, which are fabricated from hydrogel-forming polymeric matrices. Upon insertion interstitial fluid is absorbed from surrounding skin tissue, leading to hydrogel swelling (Donnelly et al., 2012a). This generates continuous, unblocked hydrogel channels, which facilitates the diffusion of the drug into and across the skin. Additionally, the rate of drug delivery can be tuned by the density of covalently crosslinked hydrogel, permitting controlled drug delivery kinetics.

This class of microneedle technology has been proposed to overcome the limitations associated with other classes of microneedles. The one-step application of hydrogel-forming microneedles linked to a drug-loaded patch overcomes the cumbersome two-step application process associated with solid microneedle skin pre-treatment. It has frequently been reported that the rate of pore closure after solid microneedle pre-treatment differs considerably, leading to considerable variation in drug delivery. Hydrogel-forming microneedles have the advantage of resisting pore closure whilst in place. In addition, the capability of using hydrogel-forming microneedles in tandem with dry reservoir systems, such as lyophilised wafers and directly compressed tablets, may expand the dose of therapeutics that can be delivered into and across the skin (Anjani et al., 2021).

Moreover, closed-loop hydrogel MNs have been developed by Yu *et al* who co-encapsulated insulin and glucose oxidase into synthetic glucose-responsive nanovesicles, which were then loaded into hydrogel-forming microneedles fabricated from crosslinked methacrylated hyaluronic acid, as seen in Figure 2 (Yu et al., 2015). *In vivo* evaluation using a mouse model showed that normoglycemia was re-established within thirty minutes and maintained for up to four hours. Furthering this, Ye *et al* developed a novel glucose-responsive insulin secreting microneedle system loaded with pancreatic β-cells and synthetic glucose-signal amplifiers. *In vivo* results highlighted that the microneedle patch promoted tight glucose control for a prolonged period of up to ten hours (G. Chen et al., 2019). Additionally, Chen *et al* developed a glucose-responsive, nondegradable microneedle fabricated from a boronate-containing hydrogel semi-interpenetrated with biocompatible silk fibroin for smart insulin delivery. The microneedle system rapidly released insulin at hyperglycaemic conditions with negligible lag time while effectively switching off the insulin release once normoglycemia is established (S. Chen et al., 2019).

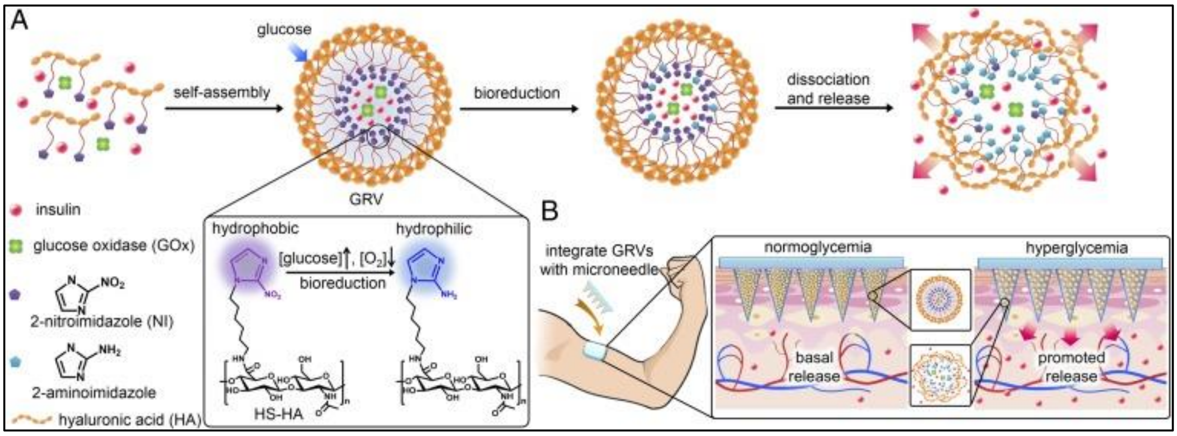


Figure 2: Development of a closed-loop 'smart insulin patch' which releases insulin from hypoxia-sensitive vesicles using glucose oxidase as a trigger. Reprinted with permission from (Yu et al., 2015).

5.2 Analysis of translational obstacles in publications related to insulin microneedles

Section 3.2 highlighted a variety of unmet translational obstacles for microneedles. Table 1 seeks to understand whether these factors, insertion efficiency, angle of insertion, dose delivery, dose adjustability, biocompatibility and therapeutic stability, have been addressed specifically in a range of insulin microneedle publications.

Table 1: A demonstration of the inconsistent reporting of translational obstacles in insulin microneedle publications

Publication title	Microneedle subtype	Microneedle insertion efficiency reported	The proportion of dose delivered reported	Angle of insertion	Dose adjustability	Material biocompatibility	Therapeutic stability
Novel lyophilized hydrogel patches for convenient and effective administration of microneedle-mediated insulin delivery *Figure 3* (Qiu et al., 2012)	Solid (pre-treatment)	N	N Permeation studies were conducted but the dose delivered was not reported as a clear proportion of the drug loading.	N	N	N	Y Stability at 0,3 & 6 months reported.
Transdermal Delivery of Insulin Using Microneedles in Vivo (Martanto et al., 2004)	Solid	N	N Estimation of insulin delivered.	N	Y Removal of microneedles after 10 seconds, 10 minutes or 4 hours, multiple concentrations of insulin solution and number of needle insertions.	N	N
3D printed microneedles for insulin skin delivery *Figure 3*	Coated	N	Y Insulin release is shown as a	N	N	Y	Y 30-day stability study.

(Pere et al., 2018)			percentage based on microneedle shape.			Biocompatible Class I resin used.	
Pharmacokinetic and pharmacodynamic evaluation of insulin dissolving microneedles in dogs (Fukushima et al., 2011)	Dissolving	N	Y Relative pharmacological availability of insulin in microneedles shown.	N	N	N	Y Stored in multiple conditions for 1 month.
Dissolving polymer microneedle patches for rapid and efficient transdermal delivery of insulin to diabetic rats *Figure 3* (Ling and Chen, 2013)	Dissolving	Y Dye study to confirm microneedle insertion.	Y In vitro drug release profile shows insulin release as a proportion of loading over time.	N	N	Y No specific study but mentions gelatine was chosen in part due to being biocompatible.	Y Storage of insulin loaded microneedles at -20, 4, 25 & 37°C for 1 month.
Hollow Metal Microneedles for Insulin Delivery to Diabetic Rats *Figure 3* (Davis et al., 2005)	Hollow	N	N Drug release is demonstrated by reduced blood glucose levels; the amount delivered is converted to units thereafter.	N	N	N	N

Minimally Invasive Insulin Delivery in Subjects with Type 1 Diabetes Using Hollow Microneedles (Gupta et al., 2009)	Hollow	N Images confirm insulin delivery through the presence of a wheal but no direct study.	N	Y Microneedles were inserted into abdominal skin at a 90° angle.	N Insulin was only administered at 1 ml/min in this study; however, this could be adapted for future use.	N	N
Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery (Yu et al., 2015)	Hydrogel	N	N	N	Y Glucose oxidase system used in 'closed-loop' system.	Y Hyaluronic acid ubiquitous in the body. A study of different concentrations of glucose-responsive vesicles showed no toxicity.	N
Smart Microneedle Fabricated with Silk Fibroin Combined Semi-interpenetrating Network Hydrogel for Glucose-Responsive Insulin Delivery (G. Chen et al., 2019)	Hydrogel	N	N	N	Y 'Smart' system using boronic acid chemistry.	Y Biocompatible silk fibroin used.	Y Stability was investigated using a degradation and morphology study.

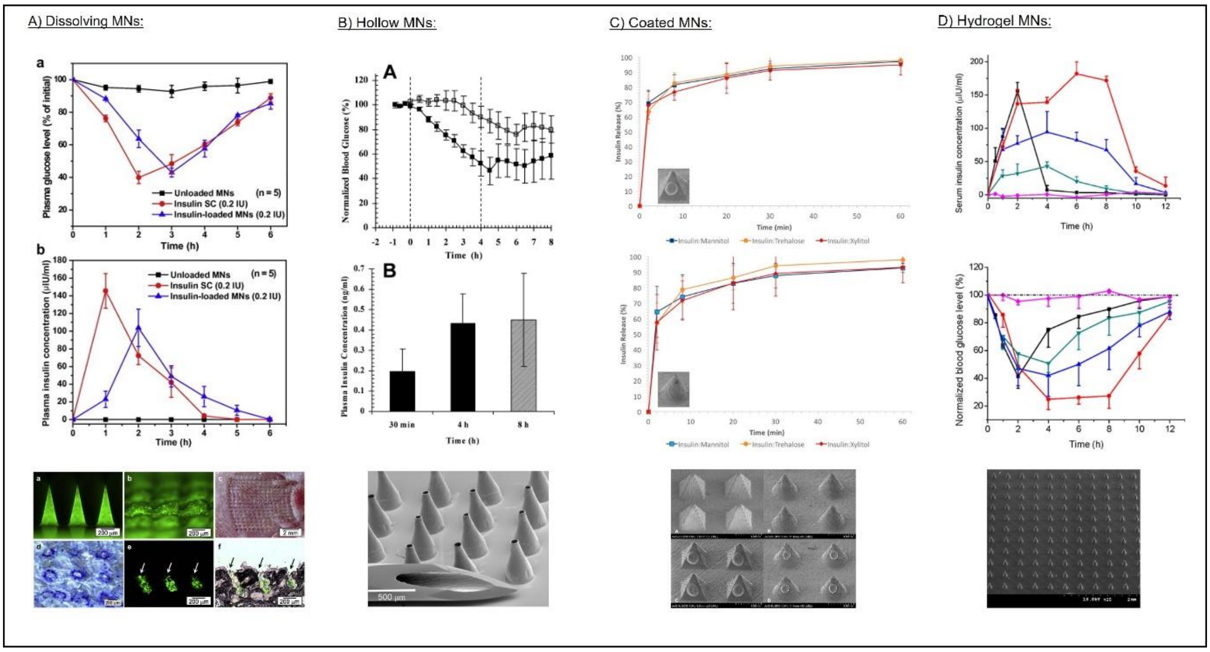


Figure 3: Demonstration of a range of insulin loaded MNs from a variety of different MN classes, as identified in Table 1. Image A) B) and D) demonstrate a reduction in blood or serum glucose and corresponding serum or plasma insulin concentrations whereas C) demonstrates insulin release from the system. Reprinted with permission from (Davis et al., 2005; Ling and Chen, 2013; Pere et al., 2018; Qiu et al., 2012)

Not surprisingly, Table 1 demonstrates that there is little consistency in the types of data that are being reported in insulin microneedle literature. Whilst each paper reported a variety of data relating to clinical translation, no publication accounted for all the factors identified in Section 3.2. Specifically, the insertion efficiency and angle of insertion of the microneedle arrays are poorly addressed.

The insertion efficiency is a key piece of data that demonstrates the proportion of a microneedle array that is being successfully inserted into the skin. Without a consistently high insertion efficiency, drug delivery will likely be incomplete or variable, potentially with drug leakage. Whilst problematic for any drug, this will render a microneedle system unsuitable for insulin delivery. Instead, publications simply infer the successful insertion of microneedles by demonstrating a reduction of blood glucose concentrations when insulin is administered. Whilst this is acceptable for proof of concept, the lack of insertion efficiency data will prove to be a sizable, if not unsurmountable, barrier to regulatory approval.

Interestingly, Table 1 also shows that the proportion of dose delivered is rarely reported in a directly and concisely. Often, the delivered dose may be derived from blood glucose levels identified in an *in* *vivo* model, as seen in Figure 3, but not as a proportion of the insulin loaded into the system, giving little context to the success of the microneedle delivery system.

Both the insertion efficiency and proportion of dose delivered are important for reproducible dosing consistency, which is essential for patients with diabetes trying to achieve and maintain a target blood glucose concentration. In order to advance in microneedle design and development, transparency with this data would be helpful.

Another poorly addressed factor is the angle of insertion of the microneedle array. Only one paper specified that the microneedles were inserted at a 90° angle relative to the skin (Gupta et al., 2009). Omission of this information in other publications leaves an unclear picture surrounding the technique used for successful microneedle insertion and may be a causative factor in poor insertion efficiency given the flexible nature of the skin. Moreover, the angle of insertion is poorly addressed in the broader microneedle literature, despite it having the potential to affect the insertion efficiency, how well the microneedle array remains inserted into the skin and the durability of the microneedles (Aggarwal and Johnston, 2004; Van Der Maaden et al., 2014b). Interestingly, the MicronJet600 exploits a 45° angle on insertion for delivery of vaccines to the skin, suggesting angle of insertion may be optimised depending on the device (Levin et al., 2015).

The biocompatibility of materials used in the microneedle system is often overlooked. Again, whilst this may not be of consequence in early work, this may cause significant hindrance in terms of transition to a clinical market. Indeed, if the material of choice is found not to be biocompatible later a suitable alternative will need to be identified. Whilst this may appear to a be trivial matter at first glance, altering the materials used will influence the mechanical characteristics and, in some instances, the drug release profile.

Lastly, it should be noted that Table 1 does not address the sterility or waste disposal of microneedles, factors which were identified in section 3.2 as playing a significant role in clinical prospect. Given that the publications in Table 1 are from early stage research, it is not surprising that these factors are not addressed. However, leaving these issues to be resolved until a later stage of development reduces the likelihood of success, especially if issues prove complex, and could lead to technologies being shelved. In future, these factors should be explored in the early stage of research to improve the probability of successful clinical translation, especially microneedle insertion efficiency and dosing consistency.

5.3 Microneedle patent review

In this section the review will highlight the patent landscape in the area of microneedle-based delivery systems for insulin. A patent search was conducted to further understand the status, trends and changes in the research and design of microneedles systems designed for the delivery of insulin. Insulin was selected as it is the most commonly prescribed therapeutic for T1DM.

A search of patents was completed using the advanced search function of Google Patents. The search term was '"microneedle" AND "insulin"'. Patents were included from 1970 – 2019. To aid analysis, the patent search was broken down into individual years, based on the date of patent filing. A total of 3,676 patents were analysed. Initially, no patents were discounted. Each patent was read before being recorded as either appropriate or inappropriate in relation to our search term. An appropriate patent was defined as including microneedle technology that was specifically designed to administer insulin.

Figure 4 demonstrates the trend in patents using the search term '"microneedle" AND "insulin"' by the filing date. There was a rise in the number of patents filed annually until 2016 before the number of insulin microneedle patents showed a downward trend. Whilst it is unclear exactly why the number of patents dropped after 2016, it should be noted the number of patents was still above a hundred per year from 2017-2019. A possible explanation could be that microneedle research started to focus on multiple kinds of microneedles, including polymer and hydrogel microneedles, which may not appear to be as suitable for insulin delivery when compared to hollow microneedles. This downward trend may also be attributed to the limited design and innovative space imposed by previous patents on inventors for the development of new microneedle-based delivery systems.

Another possibility that should be considered is the change in terminology used to describe microneedles. Recently, terms such as 'micropin' 'microarray', and 'microarray patch (MAP)', amongst others, have been coined and deemed to be a more appropriate terminology to describe the different forms of microneedles for biomedical application. A recent publication by Ingrole *et al*, which focuses on a broader patent search for microneedles, highlights this and addresses it by using 'Boolean logic' to ensure patents that featured microneedles by a different title were included (Ingrole et al., 2021).

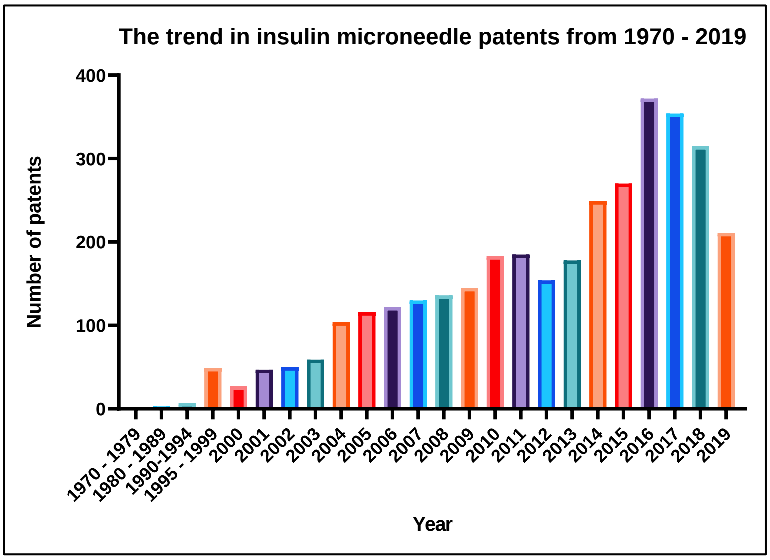


Figure 4: A graph demonstrating the trend in insulin microneedle patents from 1970 onwards according to the number of patents filed.

5.3.1 Summary of patents for insulin microneedles

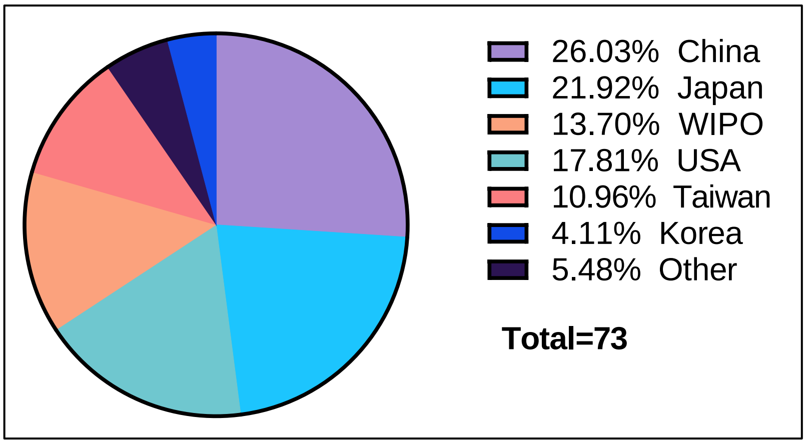


Figure 5: A graph demonstrating the distribution of countries/collectives filing relevant insulin microneedle patents.

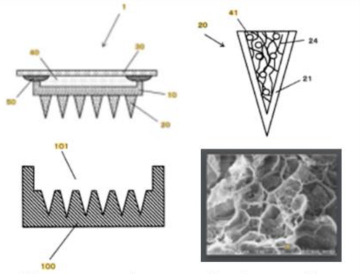
Suitable patents were recorded and analysed (Table S1 in SI). It is worth noting that out of the 3,676 patents searched, only 73 patents (1.99%) were considered suitable for tailored insulin delivery. Of the 73 relevant patents, the largest proportion (26.03%) were filed in China, as can be seen in Figure 5. This is in keeping with the general increase in the number of patents filed by China over preceding years, as interest in scientific innovation grows there. Moreover, and more specifically to insulin microneedles, some of the leading research groups for this technology are based in China.

Most frequently, it would be the case that the patent details a microneedle design, but it isn't specific to insulin delivery. In this instance, the microneedle technology described only used insulin as an example of the range of therapeutics that could be delivered rather than specifically tailoring the invention for the effective, accurate, and safe delivery of insulin for patients with diabetes. In these instances, it was impossible to understand how these patent designs could be translated to clinical use as the focus was merely proof of concept that insulin would permeate across the skin, into the systemic circulation. In more extreme instances, the patent would be completely irrelevant to the field of insulin microneedle technology but both search terms had been used in a different context and, as such, the patent showed as a result in the search.

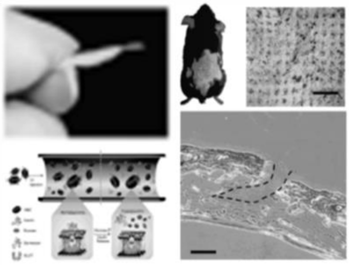
One finding was that the majority of relevant patents were filed within the last decade. This is not entirely surprising as it represents the evolution of research into microneedles with regards to clinical translation and the popularity of the field.

Despite the evidence that a wealth of research is being conducted in this field, some of which is giving rise to protected intellectual property, suggesting its value, there is yet to be a microneedle device for administration of insulin available on the market to compete with the well-established pre-filled pens, suggesting there are still design barriers to be overcome. For example, a common barrier for the commercialisation of these patents may be attributed to the need for specific and very specialised manufacturing facilities and technologies that have yet to be commonplace for the manufacture of microneedles relative to traditional dosage forms. An example of this is the high cost associated with the production of stainless-steel microneedle moulds and the variation associated with said batch manufacturing method. A movement towards continuous manufacturing may overcome these issues (Vrdoljak et al., 2016).

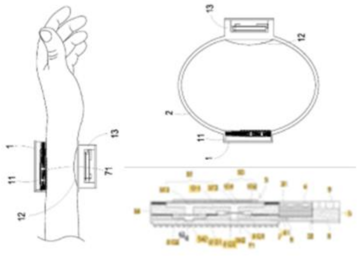
5.3.2 Exploration of strengths, weaknesses, opportunities and threats



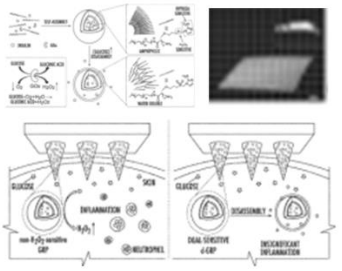
Glucose responsive composite gel composition, insulin delivery microneedle including said glucose responsive composite gel composition
US2021/0052822 A1



Glucose responsive insulin delivery compositions and methods
WO2017124102A1



Wearable liquid supplying device for human insulin injection
US20190125963A1



Patch loaded with dual-sensitive vesicles for enhanced glucose-responsive insulin delivery
US2020/0330562 A1

Figure 6: Summary of exemplar patents that meet the patent search criteria for "microneedle" AND "insulin" in the form of a closed-loop system via Google Patent (Gu and Wang, 2017; Gu and Yu, 2020; Matsumoto and Chen, 2021; Mou et al., 2019).

The large number of patents generated in this search allowed for an in-depth exploration into the status of research in this area of drug delivery. Whilst the patents lacked details of the preceding lab-based research, the format of patents allowed an overview into how the microneedles may be incorporated into a device and the concepts of the technology and science behind their development. Whilst there were patents for all types of microneedles, there appeared to be a preference for polymer and coated microneedles. Furthermore, the value of utilising biodegradable polymers to mitigate any adverse effects on the patient was recognised. Moreover, several patents detailed a design that allowed the drug-containing tip of the microneedle to break away from the rest of the microneedle, also known as arrowhead microneedles, and remain in the skin so that the drug could exert its action.

Whilst the polymer and coated microneedles detailed in the patents often listed insulin as a drug that could be utilised, it is not convincing that this has been designed rationally or specifically for insulin delivery given the inability to control the dose, particularly with the devices that see microneedle tips being rapidly separated from their supports. Such design is flawed by the need to carefully titrate the insulin dose to patients' blood glucose levels and the poor drug loading capability that usually accompanies both microneedle types. That being said, it is plausible that these devices may be more suited to basal insulin regimens, in which dose changes are less frequent.

Patents for solid microneedles were identified, particularly in a form similar to that of the Dermaroller®. Whilst it was suggested that the drug could be applied to the skin and it would flow into the channels, similar to the 'poke and patch' method, or coat the needles, it seems unlikely that these would be appropriate for insulin administration. The possibility of insulin running off the skin does not satisfy the need for accuracy with dosing and the coated microneedles would have further complications in verifying dose administration. Furthermore, the aqueous pores created by the solid microneedle devices are unpredictable in how long they may stay open, with variation between patients, complicating the dosing.

The most common issue that does not seem to be addressed by the patents revolves around dose variability and the need to tailor or change the dose with regards to the insulin administration device. This can be rationalised by inventors wanting to maintain a broad patent, offering more protection over their intellectual property with increased opportunities for revenue. However, this comes with the cost of these devices being unsuitable for insulin delivery. In only a few patents an adjustable gauge that could titrate the dose on-demand, with the majority of patents eluding to a fixed-dose mechanism instead. This was supported by the majority of patents including a list of potential pharmaceutical agents that could be loaded into a microneedle and delivered beyond the *stratum corneum*, which demonstrated few elements of rational, disease targeted design.

Often, patents would provide details to a specific feature or part of a device. Whilst this is useful with respect to potentially improving the design of an existing device, it does not aid the design of whole devices and imposes a barrier towards knowledge continuity within the field. It is, however, understandable that some inventors may opt to describe their patent in such a fashion to mitigate other competitors from developing similar products that are close to but outside the restriction of current patents. Similarly, a large proportion of patents related to moulds for making microneedles or ways to manufacture microneedles. Again, it is worth emphasising that microneedle designs are not often drug specific as the manufacturing techniques employed may not be adapted for all drugs and biologics.

However, as already mentioned in section 5.3.1, it is noted that there are multiple patents for insulin-specific microneedle systems, some of which exploit changes in pH to control insulin release, creating a closed-loop system (Figure 4). These 'smart' systems seem appealing and hold the promise and possibility of giving patients greater autonomy and flexibility in relation to their insulin regimen. Furthermore, the large number of patents relating to the detection of analytes, such as glucose, once again highlights the opportunity of incorporating a microneedle sensor into a device that can then simultaneously release the appropriate dose of insulin, without the patient having to analyse their blood glucose levels.

The most tangible threat to the technology identified in the patents are insulin pumps, which are already on the market. Although not explored in this review, it is theoretically possible that the cannulas in insulin pumps could be replaced with microneedle arrays, creating a closed-loop system, which in part, is already known to be well-received and trusted by patients. Perhaps the most significant issues surrounding this are the ability for microneedles to be retained in the skin (currently cannulas are changed approximately every three days) and the volume of liquid that can be successfully pushed through microneedles without leakage. It is noted that some of the patents that have been searched and curated are not far away from this concept. Nevertheless, there were no patents identified that have specifically considered microneedles as a replacement for cannulas with regards to an insulin pump.

Finally, another consideration is the cost of these new devices. Particularly in the instance of insulin delivery, where there is already a plethora of successfully marketed devices, the cost of developing a new device must be compared to the potential benefits. For some of the more elaborate devices reviewed, which may involve specialist input and techniques, the cost may simply be too high to attract investors. Nevertheless, if we view this through the concept of economy of scale, it could be predicted that the final market price of these devices may eventually be lower than anticipated. It may be predicted that these microneedle devices have a high market price to start with due to the complex design, intricate feedback loop and stringent quality control steps for mass production. However, as the target patient population is approximately 500 million diagnosed patients worldwide, the demand and output of the device will also be large causing the fixed cost of production to be spread over more unit of output which ultimately reduces the final market price (International Diabetes Federation, 2019).

In conclusion, our critical curation and analysis of patents highlighted that whilst there has been a rise in interest towards developing microneedle systems for the delivery of insulin, further work on the fundamental aspects of microneedle insertion and drug delivery is required before these systems can make the transition into clinical practice. Moreover, a drug-centred approach, in this case for insulin, should be taken to ensure the microneedles harness the precise properties required for delivering this unique protein. As popularity with computer modelling increases in the field of scientific research, one suggestion to exploit this would be through the use of a design of experiments (DOE) approach, to guide and highlight optimal characteristics for future device development. Such insight is pivotal to expanding our current understanding of the successes and challenges of microneedle-based delivery systems. Furthermore, the involvement of material scientists in microneedle-based research, developing novel and intelligent biocompatible materials, may help addressed the current translational hurdles associated with bringing microneedle-based delivery systems into clinical practice.

5.4 Insulin-releasing microneedles in clinical trials

Additionally, a search for clinical trials (using *clinicaltrials.gov*) was conducted to understand the status of trials involving insulin delivery via microneedles.

Currently there are no ongoing trials in this field; however it was possible to identify five relevant trials that were previously conducted.

The trial 'Insulin Delivery Using Microneedles in Type 1 Diabetes' (NCT00837512) was completed at Emory University in the USA to understand whether insulin could be delivered effectively and painlessly to children with T1DM by comparing a 900 µM microneedle device against a 9 mm subcutaneous catheter in 16 children. Conclusions drawn from this study were consistent with previously published data that suggested the microneedle insertion would be less painful than the catheter however infusion of the insulin from the microneedle was not less painful, potentially due to only being a single microneedle. Furthermore, the time to onset of the insulin was faster with administration via the microneedles, which was hypothesised to be due to localised access to the denser dermal blood circulation relative to the subcutaneous circulation (Norman et al., 2013). In addition, the transient skin inflammation, known as erythema, induced upon microneedle application promotes localised blood flow to site of administration, thus promoting the rapid uptake of insulin into the systemic circulation. Despite these findings being published in 2013, a larger study does not appear to have been completed, potentially due to a lack of interest in incorporating microneedles into pump-like devices, halting the translation to an approved device. Future studies should investigate microneedle arrays instead of single needles, where the focus should be to measure the force needed to reliably insert the array.

Another study titled 'A Pilot Study to Assess the Safety, PK and PD of Insulin Injected Via MicronJet or Conventional Needle' (NCT00602914) was sponsored by NanoPass Technologies Limited to evaluate the suitability of the MicronJet (multiple 600 µM, hollow microneedles) to deliver insulin compared to a standard needle. Another small cohort of patients (n=17) was entered into the crossover study to test the effectiveness of insulin delivery pre and post prandially. The results of the study emphasise the improved pharmacokinetic profile, as per the findings in NCT00837512 (Kochba et al., 2016). Currently, the device is approved by the FDA for subcutaneous delivery of vaccines, but not insulin. Again, this may be attributed to the few participants but also the pain scoring, which demonstrated no significant difference between the intradermal and subcutaneous delivery methods (Kochba et al., 2016).

The most recent study to be completed was 'Pharmacokinetic Comparison of Intradermal Versus Sub-cutaneous Insulin and Glucagon Delivery in Type 1 Diabetes' (NCT01684956), in 2017. This study shares many similarities with NCT00602914, although is sponsored by Massachusetts General Hospital, as it hopes to further understand the pharmacokinetic profile of insulin, and additionally glucagon, with the MicronJet device. Results for this study have been submitted but not yet published.

Crucially, this study enrolled T1DM patients, potential end-users for this device, so positive results in terms of safety, tolerability and pharmacokinetics may aid regulatory approval.

6.0 Conclusion

In conclusion, as an emerging drug delivery platform, microneedles display many patient-centred benefits, such as ease of application and painless insertion. Nevertheless, there are a multitude of factors that must be tackled prior to these devices achieving regulatory approval. Amongst these, reproducible insertion and dosing consistency remain the most poorly addressed matters.

Moreover, a more rational design of microneedle devices relating to the delivery of more complex pharmaceuticals, including insulin, is likely to accelerate the translation of microneedles into clinical use. To give one example, insulin is a drug that may require frequent dose changes, dependant on multiple factors, meaning the current design of most microneedle devices, which administer a fixed dose of drug, is unacceptable to both regulators and patients with T1DM. For this reason, amongst others, it could be argued that a hollow MN device is most favourable for the delivery of insulin and most likely to facilitate the translation of MNs from bench to bedside. However, until these fundamental matters, alongside the sterilisation, disposal and material choice are addressed, microneedles will not be a device patients or healthcare professionals can have confidence in or that regulators will approve.

Overall, as research in the field continues to progress, it is recommended that both formulators and clinicians who are actively involved in microneedle-based research consider these translational barriers, guided by end-user inputs, in both designing and evaluating microneedle devices. By doing so, a strategic and patient-centred design could make microneedle-based products a reality in clinical practice.

Acknowledgements

This work was supported by the Engineering and Physical Sciences Research Council EPSRC [grant number EP/S023054/1] via the CDT in Transformative Pharmaceutical Technologies.

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Table S1: Relevant patents for a microneedle specifically designed to deliver insulin

Patent File Date	Patent Name	Patent Number
31/5/2019	Temperature-resistant sugar-responsive gel	WO2019230961A1
9/9/2019	A kind of production method and its application of 3D printing empty micropin	CN110435139A
10/10/2019	Preparation method and application of 3D printing microneedle patch	CN110693855A
22/3/2019	Glucose responsive composite gel composition, method for producing same, insulin delivery microneedle including said glucose reactive composite gel composition, and producing method therefor	WO2019182099A1
26/8/2019	Microneedle-array patches with glucose-responsive matrix for closed-loop insulin delivery	WO2020041787A1
2/1/2019	Quick microneedle patch of a kind of phenyl boric acid water-setting matrix sugar and preparation method thereof	CN109675185A
10/9/2019	A kind of transdermal accurate drug delivery device and preparation method thereof based on micropin formula ion nestocalyx part	CN110404161A
7/5/2019	Dual chamber and gear pump assembly for a high pressure delivery system	US20190255250A1
5/10/2018	Wearable human insulin injection liquid supply device	JP2019093120A
10/10/2018	Glucose transporter inhibitor-regulated insulin for glucose-responsive insulin delivery	KR20200067173A
19/3/2018	Biodegradable microneedle array	JP6567716B1
20/11/2018	Charge switchable polymer depot for glucose triggered insulin delivery with ultra-fast response	CN111629746A

2/11/2018	Blood glucose monitoring control system	JP2019093125A
19/3/2018	Biodegradable microneedle array	TW201938199A
5/10/2018	Liquid supply device for human insulin injection	JP2019080916A
10/10/2018	Core-shell microneedle patch for h2o2 and ph cascade-triggered insulin delivery	WO2019075029A2
11/4/2018	Micro-structure skin absorption promoter, skin applyable insulin containing micro-structure skin absorption promoters, and insulin administering method using a skin-applyable insulin containing micro-structure skin absorption promoters	KR20190118865A
10/10/2018	Methods, compositions, and devices for drug/live cell microarrays	US10624865B2
9/8/2018	3D printing microneedle patch for intelligent blood sugar regulation and preparation method thereof	CN109125912B
7/3/2018	Insulin-responsive glucagon delivery patch	WO2018165294A1
2/10/2018	Wearable liquid supplying device for human insulin injection	US20190125963A1
10/8/2018	Sweat monitoring and control of drug delivery	US20180344222A1
7/12/2018	Smart adapter for infusion devices	JP2019051389A
18/7/2018	Microneedle patch for intelligently regulating blood sugar and preparation method thereof	CN108837299B
27/10/2017	Wearable human insulin injection liquid supply device	TWI666036B
27/10/2017	Wearable human insulin injects liquid feed	CN109718421A
20/11/2017	Blood sugar detecting and controlling system	TWI667016B
20/11/2017	Blood sugar monitoring control system	CN208492114U
20/11/2017	Blood sugar monitoring control system	CN109805940A
27/10/2017	Wearable human insulin injects liquid feed	CN208678059U
27/10/2017	Wearable human insulin injects liquid feed device	CN208678060U
20/10/2017	The liquid feed device of human insulin injection	CN109718462A
27/10/2017	The liquid feed device of human insulin injection	CN208405759U
27/10/2017	Wearable injection and liquid supply device for human insulin	TWM558629U
12/4/2017	Microneedle array and method for fabricating microneedle array	WO2017179615A1
27/10/2017	Liquid supplying device for human insulin injection	TW201916903A
6/11/2017	Supply system sensitive to glucose using insulin sensitive to hypoxia nancomposites	ECSP17073558A
20/11/2017	Blood glucose monitoring and control system	TWM557589U
27/10/2017	Wearable human insulin injects liquid feed device	CN109718420A
17/2/2017	Methods and compositions related to physiologically responsive microneedle delivery systems	JP2019506951A
27/10/2017	Liquid supply device for human body insulin infusion	TWN560924U
7/11/2017	Patch loaded with dual-sensitive vesicles for enhanced glucose-responsive insulin delivery	US20200330562A1
17/1/2017	Glucose responsive insulin delivery compositions and methods	US20190015515A1
5/12/2017	Core shell type microneedle device and use thereof	JP2020512283A
27/10/2017	Wearable liquid supplying device for human insulin injection	TW201916899A
8/5/2017	Ballistic microneedle infusion device	JP2017127769A

21/4/2016	Glucose-responsive insulin delivery system using hypoxia-sensitive nanocomposites	JP2018513874A
4/10/2016	Blood sugar control micro system and the automatic injection of insulin	WO2018033781A1
3/6/2016	Biosensor and method for forming same and glucose control system, method for forming the glucose control system, and method for controlling glucose thereby	WO2016200104A1
30/6/2016	Drug delivery device	KR101843265B1
11/3/2016	Portable injection device of intelligence insulin based on cloud calculates	CN205626630U
21/4/2016	Patent JP2018513874A5	JP2018513874A5
21/4/2016	Glucose-responsive insulin delivery system using hypoxia-sensitive nanocomposites	JP2018513874A
14/4/2015	Injection needle unit and liquid injection apparatus	JP2016198412A
23/9/2013	Manufacture of nonelectornic, active-infusion patch and device for transdermal delivery across skin	US10548854B2
1/2/2013	Closed-loop insulin delivery device integrating micropump and microneedle array	CN203060453U
5/11/2012	Autonomous, ambulatory analyte monitor or drug delivery device	US9603562B2
7/8/2012	Disposable array-type micro injection needle head and pre-filling injector thereof	EP2749306B1
7/7/2011	Modular microneedle transport device	WO2012013472A1
16/3/2011	Medical device for analyte monitoring and drug delivery	US9131884B2
28/11/2011	Dermal infusion set by insulin pump having a mechanized cannula insert partially integrated with the disposable activation part	ES2522933T3
10/11/2010	Easy painless drug delivery device	CN101972499B
24/11/2010	Microneedle array device	JP5718622B2
24/9/2010	Transdermal drug delivery patch system, method of making the system and method of using the system	JP5460538B2
10/12/2010	Medicament microdevice delivery system, cartridge and method of use	US8251958B2
16/12/2009	Self injection device	JP5650241B2
20/10/2009	A kind of transdermal administration kit	CN102039000B
12/2/2009	Microneedle-based pen device for drug delivery and method for using same	US8900186B2
17/12/2008	Method for manufacturing a micropump and micropump	WO2009087025A1
17/8/2007	Microneedle and microneedle patch	JPWO2008020632A1
29/8/2007	Combined sensor and infusion set using separated sites	US9968742B2
25/4/2007	Patch-like infusion device	US7678079B2
17/8/2001	Device for providing a liquid with a constant volume flow and a button for an adjustable bolus dispenser	DE60110236T2